Review Article

Reactivity and Selectivity in Lewis-Acid-Catalyzed Diels–Alder Reactions of 2-Cyclohexenones

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The reactivity, regioselectivity, *endo–exo* diastereoselectivity and diastereofacial selectivity of the Lewis-acid-catalyzed Diels–Alder reactions of 2-cyclohexenones are discussed. The *syn–anti* diastereofacial selectivity of the cycloadditions is interpreted in terms of a unifying stereoelectronic pathway and conformational effects.

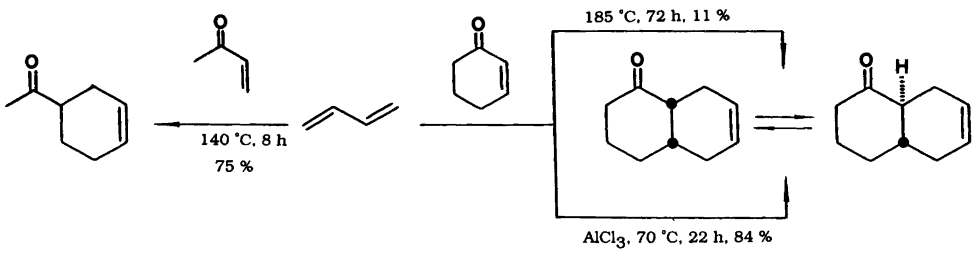
Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

Although the Diels–Alder reaction of 2-cyclohexenones with 1,3-butadienes in principle is one of the simplest and most elegant methods of rapidly synthesizing decalin systems and thus the related skeletons of more complex polycycles, until the sixties it was not widely used in the total synthesis of natural products (sesquiterpenes, tricyclic diterpenes, steroids, etc.). The generally low product yields in the Diels–Alder reaction of 2-cyclohexenones were due to the drastic reaction conditions required and discouraged the use of this methodology in favor of other annulation methods (e.g., Robinson annulation). The recent renewed interest in using 2-cyclohexenone cycloadditions as key steps in the synthetic strategy to polycycles, prompted us to review the main aspects (reactivity, regioselectivity, diastereoselectivity) of the reactions of these dienophiles.

Reactivity. In contrast with the behavior of acyclic α,β-unsaturated carbonyl compounds, 2-cyclohexenone and its variously alkylated derivatives are poor dienophiles which causes their thermal Diels–Alder reactions with 1,3-butadiene and its alkyl derivatives to require high reaction temperatures and long reaction times and to lead to poor product yields[1,2] (Scheme 1). With the discovery of Lewis-acid catalysis of the Diels–Alder reaction[3] the reactivity of these ketones toward dienes increased and the reaction conditions became milder, but the product yields remained generally low.[4] A detailed study of the reaction parameters of these reactions under aluminum chloride catalysis has overcome the yield problem, making the Diels–Alder reaction a facile, high-yielding, one-step synthesis of octalones[1,5] (Scheme 1). Whereas the products are expected to be *cis*-bicycles, those derived from 2-unsubstituted-2-cyclohexenones are often converted into *trans*-octalones under the influence of the catalyst.[1,6]

The catalyst does not affect the accepted concerted mechanism of the Diels–Alder reaction.[7] The cycloaddition of 2-phenyl-2-cyclohexenone with 1,3-butadiene catalyzed by $AlCl_3$ seems to be the sole exception; a zwitterionic intermediate has been invoked to explain the formation of *trans*-fused cycloadducts.[8]

Sometimes the catalyst causes transformations of the primary cycloadducts as in the case of the reaction of



Scheme 1.

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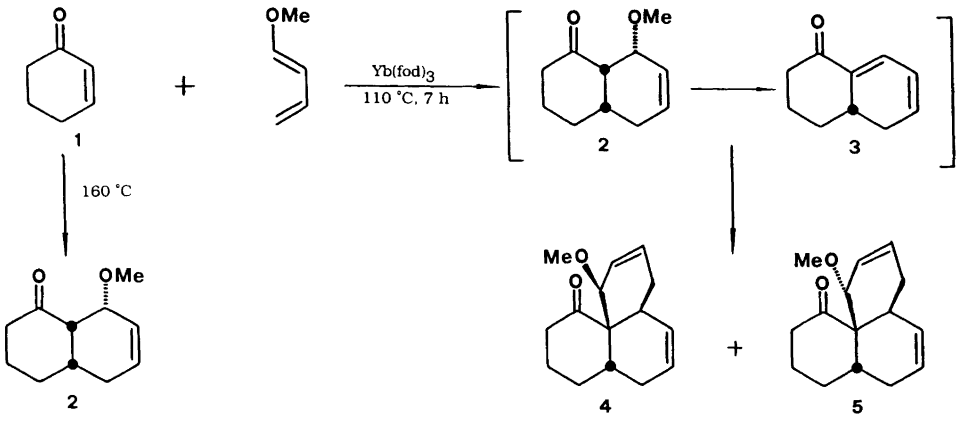


Scheme 2.

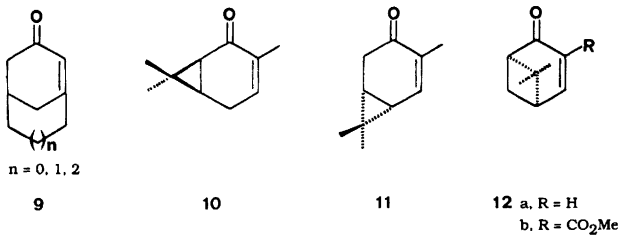
2-cyclohexenone (**1**) with (*E*)-1-methoxy-1,3-butadiene.[9] The Lewis acid induces β-elimination of methanol of the adduct **2**, and the resulting dienone **3** undergoes cycloaddition with the starting diene to afford the tricyclic adducts **4** and **5** (Scheme 2).

This is the first case of a tandem Diels–Alder reaction in which the initial monoadduct is converted into a new dienophile.

The reactivity of 2-cyclohexenones can be markedly increased by high pressure. A significant example is offered by the reactions of 3-methyl-2-cyclohexenone (**6**) with simple acyclic dienes. It had been observed that both thermal and catalyzed cycloadditions of **6** with isoprene, (*E*)-1,3-pentadiene, 2,3-dimethyl-1,3-butadiene and (*E*)-2-methyl-1,3-pentadiene do not occur at atmospheric pressure.[5] The application of high pressure (12 kbar) in combination with a Lewis acid ($EtAlCl_2$) promotes the cycloadditions (44–60%) offering a new straightforward route to *cis*- and *trans*-angularly methylated octalones in which the angular methyl group is in a 1,3-positional relationship with the keto function[10] (Scheme 3). The same marked reaction rate acceleration by high pressure has been found in the cycloadditions of 3-methyl-2-cyclopentenone with several 1,3-butadienes.[11]

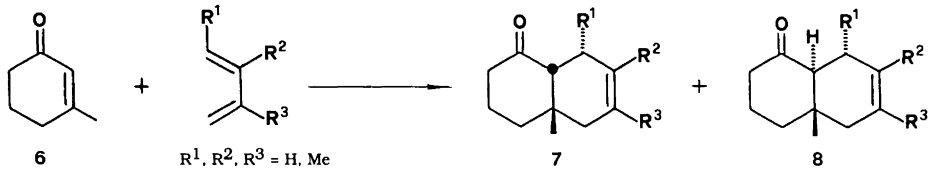
Distortion of the conjugated enone system from planarity as in bridgehead enones (**9**)[12] as well as reduced flexibility of the six-membered ring as in the cases of (+)-carenones,[13] **10** and **11**, and (+)-apoverbenone[14] (**12a**) and its 2-methoxycarbonyl derivative[15] (**12b**) influence the reactivity of the 2-cyclohexenone ring.

Electron-withdrawing groups on the cyclohexenone carbon–carbon double bond and/or donating functions on the diene increase the reaction rate,[15,16] sometimes making the catalyst and high pressure superfluous, and the reaction conditions less severe.

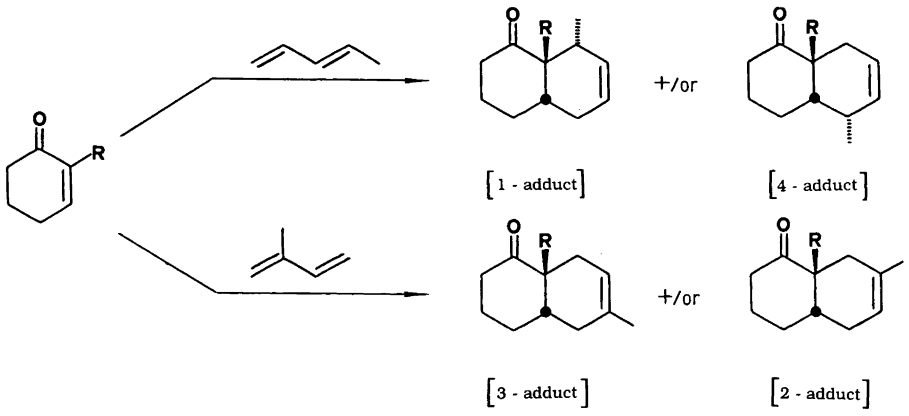


As a consequence of the ease of the Diels–Alder cycloaddition by Lewis acid catalysis and/or high pressure and/or substituent activation, the potential of the methodology became apparent, and it has been successfully and extensively applied in organic synthesis, especially in the field of natural product synthesis.[17]

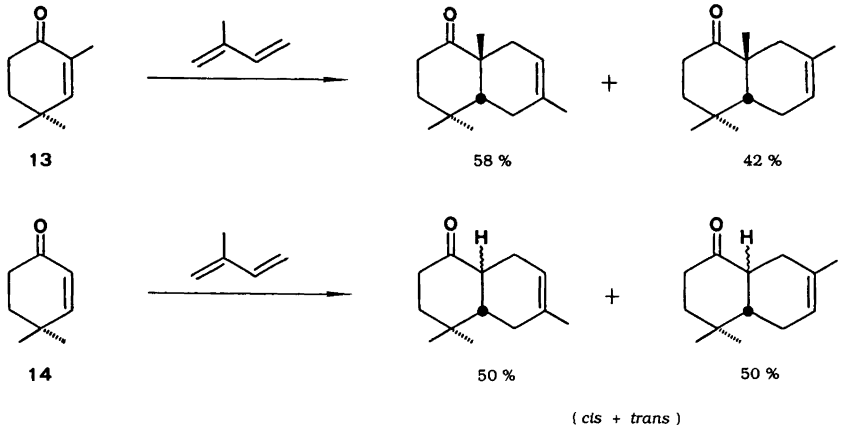
Regioselectivity. Problems of regiochemistry may arise in Diels–Alder reactions as a consequence of the use of unsymmetrically substituted dienes, as portrayed in Scheme 4. The Diels–Alder reactions of 2-alkyl-2-cyclohexenones with (*E*)-piperylene show a strong regiochemical bias toward [1]-adducts,[1,18] a phenomenon which can be explained on the basis of frontier molecular orbital theory.[19] The reactions with isoprene (with some exceptions) reveal a preference for [3]-adducts,[1,18] albeit less strongly, and those with 2-methyl-1,3-pentadiene (a piperylene- and isoprene-like compound) marked piperylene-like behavior, i.e., forming [1,3]-adducts[18] (Scheme 4).



Scheme 3.



Scheme 4.



Scheme 5.

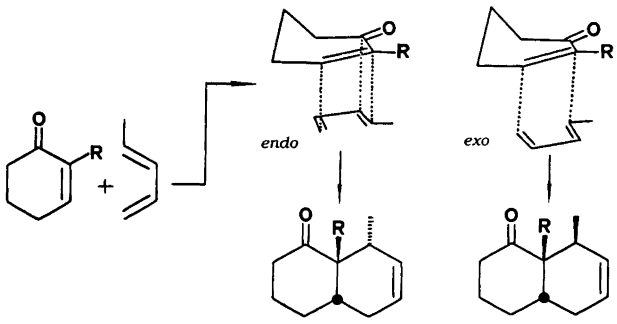
Whereas 2,5,5-trimethyl- and 2,6,6-trimethyl-2-cyclohexenones undergo Diels–Alder reactions with isoprene in such a fashion as to give mostly [3]-adducts,[18] the reactions of ketones **13** and **14** are not regioselective, leading to ca. 1 : 1 [3]- and [2]-adduct mixtures[18,20] (Scheme 5).

In order to avoid the strong repulsion between the diene and dienohile methyl groups, the addition takes place with reversed regiochemistry. The cycloadditions of 3-nitro-2-cyclohexenone with isoprene and (*E*)-piperylene show a regiochemistry reversal caused by the strong electron-attracting effect of the nitro group.[16c]

The cycloaddition of 3-methyl-2-cyclohexenone (**6**) with isoprene, (*E*)-piperylene and (*E*)-2-methyl-1,3-pentadiene under high pressure in combination with $EtAlCl_2$ as the catalyst, affords regioselectively [1]-, [3]- and [1,3]-cycloadducts, respectively.[10]

Finally, variously functionalized 1,3-butadienes show piperylene- or isoprene-like regiochemistry.[4,16a,b,21]

endo–exo *Diastereoselectivity*. The two components of a Diels–Alder reaction, approaching each other in parallel planes, may interact, *a priori*, in two different orientations affording *endo* and *exo* adducts. The terms *endo* and *exo* were initially used to designate only the stereochemistry of the adducts, not the stereochemical mode of interaction of the reactants in the transition state. This has been the source of some confusion. Tentatively, *endo* addition can be defined as that particular spatial arrangement of reactants in which the large side of the diene is under the large side of the dienophile. Conversely, in the *exo* addition the large side of one component will be under the small side of the other component[19a] (Scheme 6).

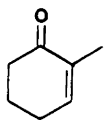


Scheme 6.

endo-Addition is known to be the preferred Diels–Alder reaction path. Thermal and Lewis-acid-catalyzed cyclo-

additions of (*E*)-piperylene, (*E*)-2-methyl-1,3-pentadiene, cyclopentadiene and 1,3-cyclohexadiene with 2-cyclohexenones unsubstituted at the olefinic carbons[1,16a,22–26] give *endo* addition. In contrast, the cycloaddition of 2-cyclohexenone (**1**) with 1-acetoxy-5-*tert*-butyldimethylsilyloxy-1,3-pentadiene affords predominantly the *exo*-adduct under high pressure conditions.[27] Usually the preferred *endo* addition is justified on the basis of transition-state stabilization by secondary orbital interactions.[19,28]

The *endo–exo* diastereoselectivity is strongly dependent on the presence of a substituent on the olefinic α-carbon of 2-cyclohexenones. In the cycloadditions of 2-methyl-2-cyclohexenone (**15**)[1,24] as well as of 2-isopropyl-2-cyclohexenone (**16**)[24] or 2-methoxycarbonyl-2-cyclohexenone (**17**)[16d] with (*E*)-piperylene 30%, 4% and 60% of the



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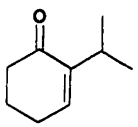

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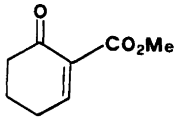

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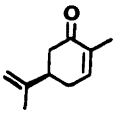
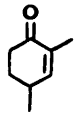
exo-diastereoselectivity, respectively, is observed. When the methyl group is on the olefinic β-carbon, as in the case of 3-methyl-2-cyclohexenone (**6**) only the *endo* addition occurs.[10] Whereas the '2-methyl effect' remains an unresolved issue, the decrease in *exo* addition observed in the reaction of ketone **16** with respect to **15** is expected for steric reasons; the lowering of *endo* product yield in the reactions of the 2-methoxycarbonyl derivative should depend on the presence of two carbonyl functions that can stabilize both *endo* and *exo* transition states.[29] The *endo–exo* diastereoselectivity in the cycloaddition of **15** with cyclopentadiene has been proposed to be controlled by the interplay between a repulsive destabilizing steric interaction of the 2-methyl group with the cyclopentadiene methylene hydrogens and the attractive secondary orbital interactions in the *endo* transition state.

As Table 1 indicates, the amount of *endo* addition for 2-methyl-2-cyclohexenone (**15**) (70%) remains relatively constant on introduction of an alkyl group at carbons 4, 5 or 6. An *endo–exo* stereochemical analysis of the dialkylated 2-cyclohexenones must take into consideration both the *syn* and *anti* addition modes (see the following section). For carvone (**18**), a 5-substituted 2-methyl-2-cyclohexenone and hence a substance undergoing exclusively *anti*-addition (see the next section), the *endo–exo* ratio is nearly independent of the nature of the diene.[30]

For 2,6-dimethyl-2-cyclohexenone (**19**), a compound undergoing both *syn*- and *anti*-addition (see the next section), the *endo–exo* ratio of the *syn*-addition is very similar to that of the *anti*-addition in view of the minimal difference in non-bonded interactions in the transition states of the two reaction modes.[31] The same relationship holds for the reaction of 2,4-dimethyl-2-cyclohexenone (**20**) with (*E*)-piperylene.[31] However, in the reaction of the latter ketone with (*E*)-2-methyl-1,3-pentadiene, the formation of *endo* product within the *syn*-addition frame is diminished greatly as a consequence of the non-bonded interaction between the 4-methyl group of the ketonic ring and the 2-methyl group of the diene in the transition-state complex.[24]

Table 1. % *endo* Diastereoselectivity of dialkylated-2-cyclohexenones.

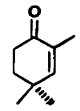
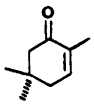
Dienophile	Diene	% of Adducts					
		syn		*anti*			
		endo	*exo*	*endo*	*exo*	*endo*	Ref
 18		(4) (3)	(1) (0)	71 77	24 20	75 80	30
 19		(50)	15	25	10	75	31
 20		40 4	9 13	39 63	12 20	79 67	31

A *gem*-dimethyl unit on the 2-methyl-2-cyclohexenone nucleus affects the *endo–exo* product ratio differently when located at various sites (Table 2). In the case of the geminal substituents being attached to carbons 5 or 6, i.e., ketones **21** and **22**, respectively, a high percentage of *endo*-addition has been observed in the reactions with (*E*)-piperylene[24] and (*E*)-2-methyl-1,3-pentadiene and a very low percentage of *endo*-addition in the reaction with cyclopentadiene.[25] 2,4,4-trimethyl-2-cyclohexenone (**13**) gives a high percentage of *endo*-adduct with (*E*)-piperylene,[24] but a much lower percentage with cyclopentadiene[25] and dimethylated butadiene. The last fact can be interpreted on the basis of the effect of the energetically unfavorable non-bonded interaction between the equatorial 4-methyl group and the diene's 2-methyl group on the transition state of a cycloaddition in an antiparallel mode (see the next section).

Conformationally rigid enones such as (+)-apoverbenone (**12a**)[14] and its 2-methoxycarbonyl derivative (**12b**)[15] and (+)-3-caren-2-one (**10**)[13] which can be formally considered as di- and tri-substituted 2-cyclohexenones, give 57%, 0% and 100% *endo*-adduct, respectively, in the cycloaddition with (*E*)-piperylene and (*E*)-1-methoxy-1,3-butadiene.

Diastereofacial selectivity. In addition to the *endo–exo* diastereoselectivity, another aspect of the stereoisomerism of the Diels–Alder reactions of 2-cycloalkenones becomes important when the two faces of the π-bond system of the interacting diene and/or ketone are not equivalent. This phenomenon manifests itself whenever the plane through the multiple-bond system of neither one nor both of the

Table 2. % *endo* Diastereoselectivity of *gem*-dimethyl-2-methyl-2-cyclohexenones.[24,25]

Dienophile			
 **13**	97	41	60
 **21**	97	86	29
 **22**	73	78	42

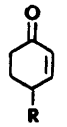
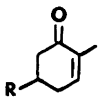
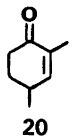
reactants represents a symmetry plane. In this case the cycloaddition gives two diastereoisomers and the two ways of addition are called *syn* and *anti* with respect to the group, or structural moiety, that makes the two faces different.[19a] 2-Cyclohexenones functionalized at C-4 and/or C-5 and/or C-6, are dienophiles having this property; earlier this phenomenon was mostly studied with unsymmetrical, rigid dienes.[32]

One of the important parameters in any evaluation of the stereochemistry of the Diels–Alder reaction of substituted 2-cyclohexenones, whose substituent(s) makes the two ring faces dissimilar, is the direction of diene attack with respect to the substituent(s). Heretofore it has been assumed that steric factors govern the reaction outcome.[33] Whereas this idea is able to justify the result of the **12** → **23**,[14,15] **10** → **24**[13] and **11** → **25**[13] transformations, it is less acceptable for the **26** → **27**[22,34] conversion, wherein the diene–dienophile interaction takes place *anti* to the methyl group distant from the reaction site, and becomes untenable as an explanation for the formation of a ca. 1 : 1 mixture of *syn* (**29**) and *anti* (**30**) primary adducts in the Diels–Alder cycloadditions of 4-methyl-2-cyclohexenone (**28**)[23] (Scheme 7).

A recent broad study of the Diels–Alder reactions of 4-, 5-, and 6-monosubstituted 2-cyclohexenones with 1,3-butadiene, isoprene and (*E*)-piperylene has furnished much data (Table 3) which help to understand the parameters controlling the diastereofacial selectivity of these conformationally mobile systems and then to predict the reaction diastereoselectivity of more complex 2-cyclohexenone derivatives.[31]

The explanation is based on the hypothesis that the cycloaddition takes place in a one-step reaction[19] with an unsymmetrical, non-synchronous transition state[35] in which the σ-bond formation with the β-carbon of the α,β-unsaturated ketone takes place in advance of that at the α-carbon site and the diene attack at the dienophile's β-carbon occurs (in the absence of strong steric interactions) along a direction antiparallel[36] to the pseudo-

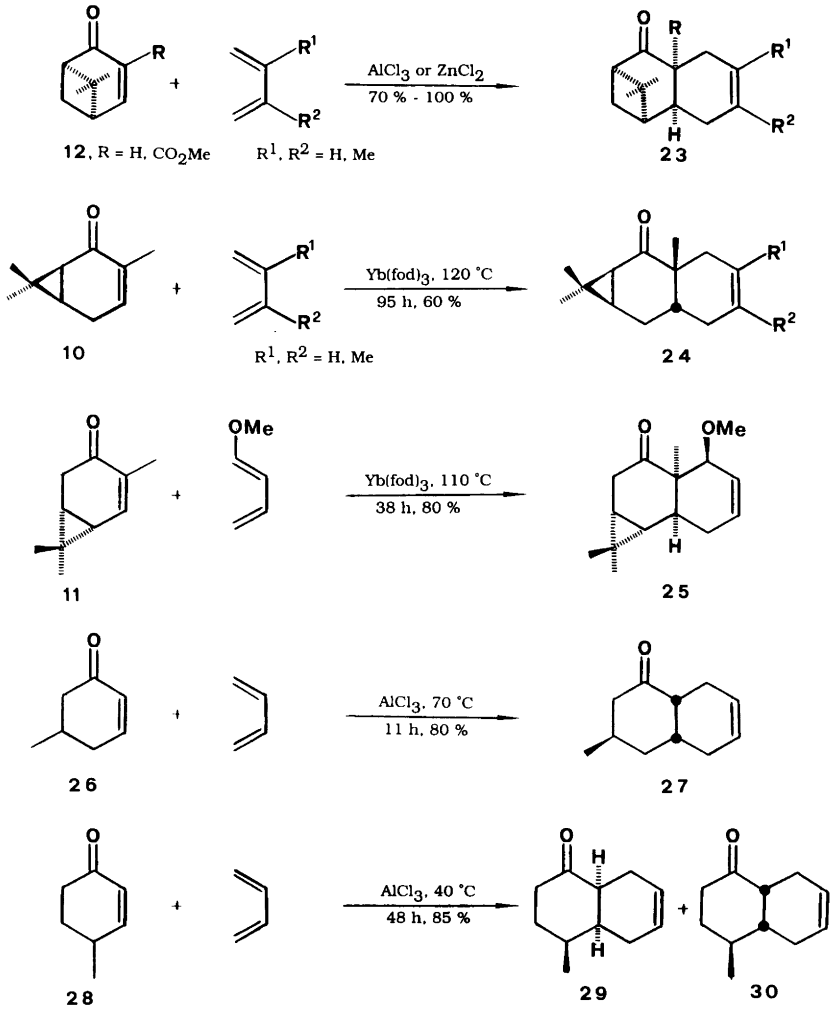
Table 3. anti Diastereofacial selectivity (%) of alkylated 2-cyclohexenones.[14,31]

Dienophile	R			
 **31**	Me	55	90	49
	i-Pr	67	91	61
	t-Bu	100	100	100
 **32**	Me	96	97	96
	i-Pr	92	92	98
	t-Bu	97	91	97
 **33**			35	33
 **20**		55	85	51
 **18**	Me	100		
	isopropenyl	90	90	95
 **19**			64	35
 **12a**			100	100

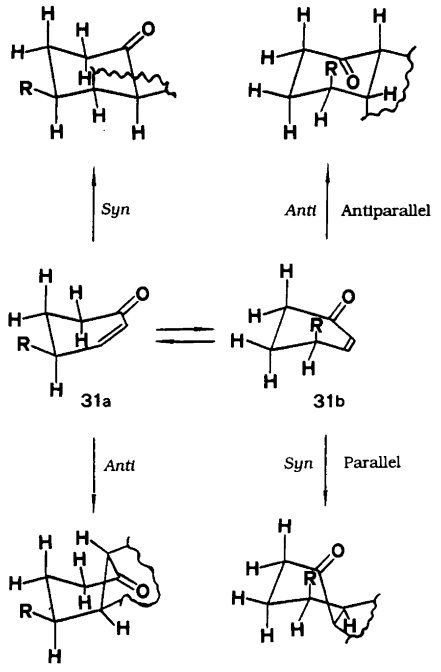
axial bond at the cyclohexenone γ-carbon over a parallel approach.[37,38] Moreover, it is known that Lewis acid–ketone complexation does not affect the conformational equilibrium of 2-cyclohexenones.[39]

As Scheme 8 (representing the Diels–Alder reaction of a 4-alkyl-2-cyclohexenone)[40] illustrates, the anti-parallel interaction on either of the two 2-cyclohexenone envelope conformers[31] involves a chair-like transition state, whereas the parallel approach necessitates the adoption of a less favorable boat-like transition state.

In the case of 4-methyl-2-cyclohexenone (R = Me, Scheme 8) the conformer equilibrium is ca. 4 : 1 in favor of the form containing an equatorial methyl function (**31a**, R = Me).[39] However, this conformer is less reactive than its equilibrant, since a Diels–Alder reaction in an antiparallel manner generates a 1,2-*gauche* interaction



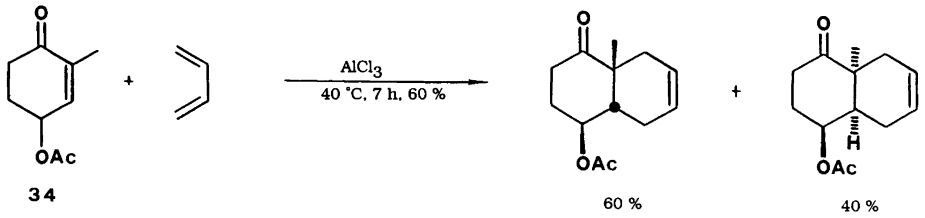
Scheme 7.



Scheme 8.

between the 4-methyl group and the developing axial carbon–carbon bond at C(3) upon the system. The conformer concentration vs. reactivity factors balance in such a fashion as to lead to ca. 1 : 1 mixtures of *syn* and *anti* adducts in the reactions of 4-methyl-2-cyclohexenone (**31**, R = Me) with 1,3-butadiene or (*E*)-piperylene.[41] Increasing the unfavorable 1,2-*gauche* interaction by enlarging the size of the 4-alkyl group (**31**, R = *i*-Pr or *t*-Bu) or imposing yet other non-bonded interactions on the 4-methyl function, e.g., by the methyl group of the diene in the case of reactions with isoprene (in *endo* additions), pushes the Diels–Alder reaction toward *anti* adducts (Table 3).

In as much as the conformational equilibrium of 6-methyl-2-cyclohexenone (**33**) is similar to that of its 4-methylated isomer, but the aforementioned 1,2-*gauche* interaction is missing from its cycloaddition in an antiparallel mode, the reaction is expected to emanate preferentially from the equatorially methylated conformer, thus leading mostly to *syn* products. The explanations of the *syn–anti* diastereoisomerism of the Diels–Alder reactions of 4- and 6-alkylated 2-cyclohexenones now



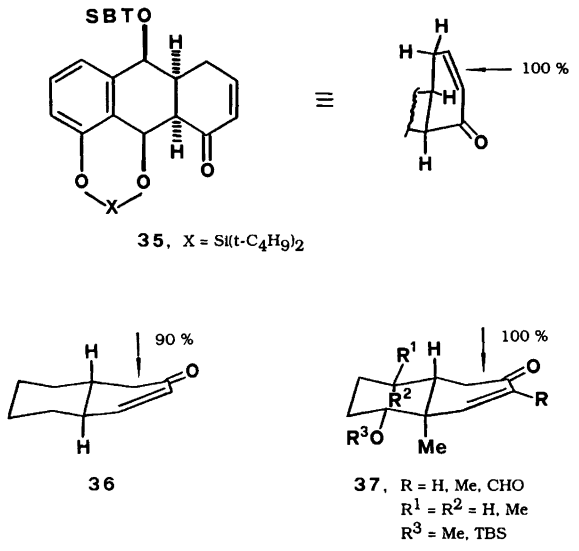
Scheme 9.

permit a ready interpretation of the high *anti* diastereofacial selectivity of 5-alkyl-2-cyclohexenones (Table 3). Since the activation energy of the cycloaddition of the latter in an antiparallel sense operating on the conformer with an axial alkyl group would be prohibitive in view of the attendant 1,3-diaxial non-bonded interaction between the alkyl substituent and the developing axial carbon–carbon bond at C(3), the reaction funnels through the equatorially alkylated conformer ending up with *anti* adducts independent of substituent size.

The ideas expressed above for the Diels–Alder reactions of 4-, 5- and 6-monoalkylated 2-cyclohexenones explain the diastereofacial selectivity observed in the reaction of 4-acetoxy-2-methyl-2-cyclohexenone (**34**) with 1,3-butadiene (Scheme 9)[42] and can be applied to stereochemical analyses of structurally more complex cyclohexenones, as exemplified by the following three cases.

It has been shown that the cyclohexenone derivative **35** (Scheme 10) undergoes boron trichloride catalyzed cycloaddition in high yield, exclusively in the direction depicted by the arrow on the formula.[43] The ketone is the equivalent of an equatorially 5-alkylated, axially 6-alkylated 2-cyclohexenone constrained to one conformation and thus ideally suited to *anti* addition in an antiparallel mode.

The preferred diene attack (90%) in the Diels–Alder



Scheme 10.

reaction of the *trans*-bicyclic ketone **36** with (*E*)-piperylene occurs along the route depicted by the arrow in the formula[44] (Scheme 10). The octalone **36** corresponds to a conformationally rigid 2-cyclohexenone equatorially alkylated at both carbons 4 and 5.

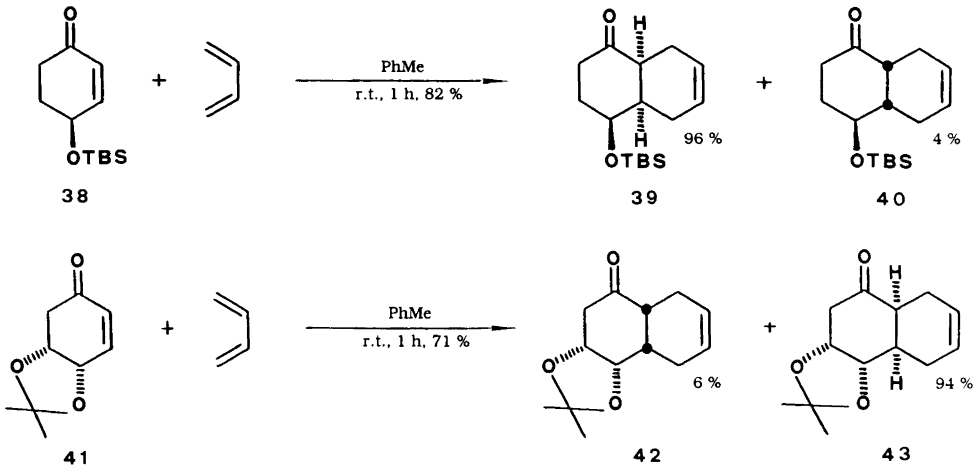
Cycloaddition in an antiparallel mode requires *anti* addition with respect to the C(5) substituent and *syn* addition with regard to the C(4) attachment of the neighboring ring. Since the latter requirement introduces an energetically unfavorable 1,2-*gauche* interaction between the C(4)-connected methylene group and the developing, axial carbon–carbon bond at the olefinic β-carbon site, ca. 10% of the reaction follows the less favorable, parallel path, i.e., diene attack from the opposite side of the ring system. Whereas in the monocyclic series the latter reaction mode could be overcome by the cycloaddition occurring in an antiparallel fashion on the less stable conformer (**31b**, Scheme 8), ketone **36** does not have the option of establishing a conformational equilibrium of the **31a** → **31b** type (Scheme 8).

Finally, *trans*-bicyclic ketones **37** have shown to undergo Diels–Alder reactions exclusively on the ring face indicated by the arrow in the formula.[45]

Since the enone **37** differs from ketone **36** mainly by the presence of an angular methyl group, all the arguments put forward to justify the stereochemical outcome of the Diels–Alder reaction of the ketone **36** should apply to the cycloaddition of ketones **37**, except for the expected suppression of the addition by the parallel mode in view of the added factor of an unfavorable 1,2-eclipsed interaction in such a reaction path between the angular methyl group and the incipient new bond at the olefinic β-carbon center. Thus the reaction takes place in a fully antiparallel fashion on the face of the bicycle shown in the formula.

Recently Danishefsky *et al.*[46] reported that the aluminum chloride catalyzed Diels–Alder reaction of 4-OTBS cyclohexenone **38** with 1,3-butadiene at room temperature gives mainly the adduct **39** arising from *syn* addition (Scheme 11) whereas the *anti*-addition ketone **40** is the principal product when the aluminum chloride catalyzed Diels–Alder reaction is carried out at 40°C for 4 h. Thus in the cycloaddition of the enone **41** with 1,3-butadiene in presence of aluminum chloride catalyst, the *anti*-adduct is also the major component of the reaction mixture (Scheme 11).

The prevalent *syn*-addition of 4-OTBS-2-cyclohexenone (**38**) has not been explained in the light of a cycloaddition governed by stereoelectronic and conformational factors;



38 39 40

41 42 43

Scheme 11.

the authors hypothesize that: 'in Lewis acid catalyzed processes, the importance of stabilizing the emerging σ* orbital at the β carbon by interaction with the σ bonds of the γ carbon becomes particularly critical. Carbon–carbon bond formation *syn* to the electron-withdrawing resident OR group places the emerging σ* orbital *syn* to the σCH bond at the γ carbon. In the alternate sense of attack, where the nucleophile would attack *anti* to the OR group, a less favorable and possibly destabilizing *syn* interaction between the emerging σ* orbital at the β carbon and the electron σC–OR function at the γ carbon would be engendered. Therefore, *syn*-face addition is favored'.

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